

RECEIVED

DEC 05 2003

TECH CENTER 1600/2900

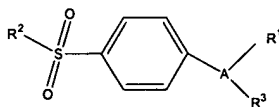
PHA4151.7 (2916/4)
PATENT

IN THE CLAIMS

Claims 1-8. (Cancelled)

Claim 9. (Previously presented) A composition comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor, a 5-lipoxygenase inhibitor and an immunosuppressive drug selected from antiproliferation agents, antiinflammatory-acting compounds and inhibitors of leukocyte activation.

Claim 10. (Previously presented) The composition of Claim 9 wherein the cyclooxygenase-2 inhibitor is selected from 5-bromo-2-(4-fluorophenyl)-3-[4-(methanesulfonyl)phenyl]-thiophene, N-[2-cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1,1-dioxide-4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I wherein:



(I)

wherein A is a 5-or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carbocyclic rings;

wherein R¹ is at least one substituent selected from heterocyclo, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R² is selected from alkyl, and amino; and

wherein R³ is a radical selected from halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclooxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclo, cycloalkenyl, aralkyl, heterocycloalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminomethyl, N-aralkylaminomethyl, N-alkyl-N-aralkylaminomethyl, N-alkyl-N-arylaminomethyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

Claim 11. (Previously presented) The composition of Claim 9 wherein the 5-lipoxygenase inhibitor is selected from (R*,S*)-4,4-(2,3-dimethyl-1,4-butanediyl)bis-1,2-benzenediol, (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, N-(1-Benzo[b]thien-2-yl-ethyl)-N-hydroxyurea, 4-[2',4'-difluorobiphenyl]-4-oxo-methyl-butanic acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, (R)-(+)-N-[3-[5-(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl) acrylamide, (R)-2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentyl-acetic acid, dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, 2-butyl-4-methoxy-1-

naphthalenol-acetate, N'-[[2-[2-[(4-chlorophenyl)thio] ethoxy]-3-methoxy-5-[(2R,5R)-tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl] phenyl]methyl]-N-hydroxy-N-methyl-urea, 2,3,5-Trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone, 4,6-dimethyl-2-[(6-phenyl hexyl)amino]-5-pyrimidinol phosphate (1:1) (salt), 4-(2-quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, 4-[(4-fluorophenyl) methyl]-2-[hexahydro-1-(2-phenylethyl)-1H-azepin-4-yl]-1(2H)-phthalazinone, 3-[1-(4-chlorobenzyl)-3-*t*-butyl-thio-5-isopropylindol-2-yl]-2, 2-dimethylpropanoic acid, [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2, 3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, 6-[[4-(4-chlorophenoxy) phenoxy]methyl]-1-hydroxy-4-methyl-2(1H)-pyridinone, 10-(3-chlorophenyl)-6,8,9,10-tetrahydro- benzo[b][1,8]naphthyridin-5(7H)-one, 5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, 1-[[5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl]-4-diphenylmethoxypiperidine, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone, 2-amino-5-hydroxy-8-methylnonyl ester-benzoic acid, 3,6-dimethoxy-1,2-dimethyl-9H-carbazol-4-ol, 6-diazo-3-methyl-4-[(1E)-1,3,5-trimethyl-1-hexenyl]-2,5,7,8(1H,6H)-quinolinetetrone, N-[2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea, (Z)-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-2-imino-4-thiazolidinone- methanesulfonate salt, 4-[4,6-bis-*t*-butyl-5-hydroxy-2-pyrimidinyl]-1,3-dihydro-5-methyl-2H-imidazol-2-one, 6-hydroxy-5,7-dimethyl-2-methylamino-4-(3-pyridylmethyl)-benzothiazole, N-[2-(4-(benzhydryloxy)piperidino)ethyl]-3-hydroxy-5-(3-pyridylmethoxy)-2-naphthamide, 2,2-dibutyl-1,2,3,4-tetrahydro-5-(2-quinolinylmethoxy)-1-naphthalenol, (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid, 1,6-anhydro-3-C-[6-[[[7-cyano-5-(3-furanyl)-2-naphthal enyl]oxy]methyl]-2-pyridinyl]-2,4-dideoxy-*b*-D-threohexopyranose, 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxy phenyl]methylene]-3-(methylamino)-4-thiazolidinone, 5-[[3,5-bis(1,1-dimethyl ethyl)-4-hydroxyphenyl]methylene]-4-thiazolidinone, (S)-N-hydroxy-N-(2,3-dihydro-6-

phenylmethoxy-3-benzyofuranyl)-urea, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, 2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy)methyl]-1-ethyl-2-quinolone, 1,2-dihydro-n-(2-thiazolyl)-1-oxopyrrolo(3,2,1-kl)phenothiazine-1-carboxamide, tetrahydro-1-phenyl-1,2,4-triazin-3(2H)-one, N-[1-(3-Furyl)ethyl]-N-hydroxyurea, N-hydroxy-N-[1-[4-(phenylmethoxy)phenyl]ethyl]-acetamide, 1-[4-[3-[4-[bis(4-fluorophenyl)hydroxymethyl]-1-piperidinyl]propoxy]-3-methoxyphenyl]-ethanone, mono[2,6-dimethyl-4-[(1E)-2-(2-thienyl)ethenyl]phenyl]-butanedioic acid, 2,6-bis(1,1-dimethylethyl)-4-[2-(3-pyridinyl)ethenyl]-phenol, 2,6-dimethyl-4-[2-(2-thienyl)ethenyl]-phenol, 9-phenylnonanophydroxamic acid, 4-hydroxy-3-methoxy-1,2-dimethylcarbazole, N-hydroxy-N-[1-methyl-3-(3-phenoxyphenyl)-2-propenyl]-acetamide, 2-phenylhydrazide-benzenecarboximide acid, 4-(cyclohexyl methylamino)-1,2-naphthalenediol, diacetate ester, (2E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl]-N-hydroxy-N-methyl-2-propenamide, N-hydroxy-N-[(6-phenoxy-2H-1-benzopyran-3-yl)methyl]-urea, N-[(6-(4-fluorophenoxy)-2H-1-benzopyran-3-yl)methyl]-N-hydroxy-N-methyl-urea, methyl 2-[(3,4-dihydro-3,4-dioxo-1-naphthalenyl)amino]-benzoate, monohydrobromide-6-(2,2-dimethylhydrazino)-5,6,7,8-tetrahydro-1,2-naphthalenediol, 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione, choline salt, 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione, 3',4',5-trihydroxy-6,7-dimethoxyflavone, 3,5,6-trimethyl-1,4-dione- 2-(12-hydroxy-5,10-dodecadiynyl)-2,5-cyclohexadiene, 2-benzyl-1-naphthol, N-methoxy-3-(3,5-di-tert-butyl-4-hydroxybenzylidene pyrrolidin-2-one, 6-hydroxy-2-(4-sulfamoylbenzylamino)-4,5,7-trimethylbenzothiazole hydrochloride, 4-[(1E)-2-(4-fluorophenyl)ethenyl]-2,6-dimethylphenol, 1,6-diol, 4-(hydroxymethyl)-7-methyl-8-[3-methyl-3-(3-methylbutyl) oxiranyl]-9H-carbazole, 5-(3-phenylpropyl)-2-thiophenepentanoic acid, 4,5-dihydro-5-methyl-1-(4,5,6,7-tetrahydro-2-benzothiazolyl)-1H-pyrazol-3-amine, 4-[(2E)-3-(3,4-dihydroxyphenyl)-2-propenoate]-2-(3,4-dihydroxy phenyl)ethyl-6-O-(6-deoxy-a-L-

mannopyranosyl)- β -D-Glucopyranoside, N-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-amine, 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether, 2-N-heptyl-4-hydroxyquinoline-N-oxide, 4-bromo-2,7-dimethoxy-3,4-phenothizin-3-one, 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, 3-hydroxy-5-trifluoromethyl-N-(2-(2-thienyl)-2-phenyl-ethenyl)-benzo(b)thiophene-2-carboxamide, 2-[(4-methoxyphenyl)methyl]-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol, [[4-(4-chlorophenyl)-1-[4-(2-quinolinylmethoxy)phenyl]butyl]thio]-acetic acid, N-hydroxy-N-methyl-3-[2-(methylthio)phenyl]-2-propenamide, 3-(1((4-chlorophenyl)methyl)-3((1,1-dimethylethyl)thio)-5(quinolin-2-yl-methyl-oxy)-1H-indol-2-yl)-2,2-dimethyl-propanoate, N-hydroxy-14-methyl-N-nitroso-1-pentadecanamine, 2-amino-4-[(4-methylphenyl)thio]-phenol hydrochloride, (2E,11Z,14Z)-N-[2,3-dihydro-3-(1H-tetrazol-5-yl)-1,4-benzodioxin-5-yl]-N-methyl-2,11,14-eicosatrienamide, (2E,11Z,14Z)-N-[4-hydroxy-2-(1H-tetrazol-5-yl)-8-quinolinyl]-2,11,14-eicosatrienamide, (E)-2,6-bis(1,1-dimethyl-ethyl)-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl]-phenol, 2-[3(1-hydroxyhexyl)phenoxy-methyl]-quinoline hydrochloride, N-hydroxy-N-methyl-7-propoxy-2-naphthaleneethanamine, methyl-2-[[3-(1-hydroxypentyl)phenoxy]methyl]-benzoic acid (ester), α -pentyl-3-(2-quinolinylmethoxy)-benzenemethanol, N-hydroxy-N-methyl-4-(phenylmethoxy)-benzeneacetamide, 3-(3,5-bis(1,1-dimethyl)-4-hydroxyphenyl)thiol]-N-methyl-N-[2-(2-pyridinyl)-propanamide], (R*, S*)-1-methylpropoxy]-[(1R,2S)-2-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-acetic acid, 2-(4-fluorophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole, 6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole, 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole, (7E)-8-(2-naphthyl)-5,6-trans-5,6-methano-7-octenoic acid, (2E,4E)-N-[2-[4-(diphenyl methoxy)-1-piperidinyl]ethyl]-5-(4-hydroxy-3-methoxyphenyl)-2,4-pentadienamide, (2E)-N-[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]-3-(4-hydroxy-3-methoxy phenyl)-2-propenamide, (2E)-N-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-3-(4-hydroxy-3-methoxy phenyl)-2-propenamide, (2Z,5Z,8Z,11Z,14Z,17Z)-N-[4-[(2E)-3-

(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]butyl]-2,5,8,11,14,17-eicosahexaenamide, (2E)-N-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]ethyl]-3-(4-hydroxy-3-methoxyphenyl)-2-propenamide, 2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methylindole, 1,8-diethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)-pyrano[3,4-b]indole-1-acetic acid, 2-[(1-naphthalenyloxy)methyl]-quinoline, 1,1,1-trifluoro-N-[3-(2-quinolinylmethoxy)phenyl]-methanesulfonamide, α -methyl-6-(2-quinolinylmethoxy)-2-naphthalene-acetic acid, and 1-butyl-5-hydroxy-2-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-indole-3-carboxamide, hydrochloride.

Claim 12. (Previously presented) The composition of Claim 11 wherein the 5-lipoxygenase inhibitor is selected from (R*,S*)-4,4-(2,3-dimethyl-1,4-butanediyl)bis-1,2-benzenediol, (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, N-(1-Benzo[b]thien-2-yl-ethyl)-N-hydroxyurea, 4-[2',4'-difluorobiphenyl]-4-oxo-methyl-butanic acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, (R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl) acrylamide, (R)-2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentyl-acetic acid, dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, 2-butyl-4-methoxy-1-naphthalenol-acetate, N'-[[2-[2-[(4-chlorophenyl)thio] ethoxy]-3-methoxy-5-[(2R,5R)-tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl] phenyl]methyl]-N-hydroxy-N-methyl-urea, 2,3,5-Trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone, N-[2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea, 4,6-dimethyl-2-[(6-phenyl hexyl)amino]-5-pyrimidinol phosphate (1:1) (salt), 4-(2-

quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, 4-[(4-fluorophenyl) methyl]-2-[hexahydro-1-(2-phenylethyl)-1H-azepin-4-yl]-1(2H)-phthalazinone, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, 3-[1-(4-chlorobenzyl)-3-*t*-butyl-thio-5-isopropylindol-2-yl]-2, 2-dimethylpropanoic acid, (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-*cd*]indol-2-yl]ethoxy]-butanoic acid, [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2, 3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, 6-[[4-(4-chlorophenoxy)phenoxy]methyl]-1-hydroxy-4-methyl-2(1H)-pyridinone, 10-(3-chlorophenyl)-6,8,9,10-tetrahydro- benzo[*b*][1,8]naphthyridin-5(7H)-one, 5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide, 1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine, 2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy]methyl)-1-ethyl-2-quinolone, and 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone.

Claim 13. (Previously presented) The composition of Claim 12 wherein the 5-lipoxygenase inhibitor is selected from (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, N-(1-Benzo[*b*]thien-2-yl-ethyl)-N-hydroxyurea, 4-[2',4'-difluorobiphenyl]-4-oxo-methyl-butanic acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, N-Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, (R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, N-[2-[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyloxy]ethyl]-N-hydroxy-urea, dihydro-4-(3,5-di-*tert*-butyl-

4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, 4-(2-quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid, [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, 1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine, 2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-ethyl-2-quinolone, and 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone.

Claim 14. (Previously presented) The composition of claim 10 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, cyclopentenyl, phenyl, and pyridyl; wherein R¹ is selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy-carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R² is selected from lower alkyl and amino; and wherein R³ is a radical selected from halo, lower alkyl, oxo, cyano, carboxyl, lower cycloalkyl, heteroaryloxy, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclo, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, heteroaryloxy, alkoxy-carbonyl, aminocarbonyl, alkylaminocarbonyl, alkylamino, aminoalkyl, alkylaminoalkyl, aryloxy, and aralkoxy.

Claim 15. (Previously presented) The composition of Claim 14 wherein A is selected from oxazolyl, isoxazolyl, dihydrofuryl, imidazolyl, and pyrazolyl; wherein R¹ is

selected from 5- and 6-membered heterocyclo, and aryl selected from phenyl, biphenyl and naphthyl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R² is amino; and wherein R³ is a radical selected from oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclo, lower hydroxyalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenyloxy, and lower aralkoxy.

Claim 16. (Previously presented) The composition of Claim 15 wherein A is selected from oxazolyl, isoxazolyl, imidazolyl, and pyrazolyl; wherein R¹ is phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, trifluoromethyl, cyano, carboxyl, methoxycarbonyl, hydroxyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N-dipropylamino, butylamino, methyl-N-ethylamino, nitro, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and methylthio; wherein R² is amino; and wherein R³ is a radical selected from oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxylmethyl, hydroxypropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethyloxy,

aminocarbonyl, N-methylaminocarbonyl, N-dimethylaminocarbonyl, N,N-methylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, and phenyloxy.

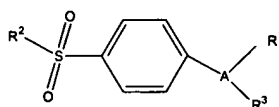
Claim 17. (Previously presented) The composition of Claim 16 wherein the cyclooxygenase-2 inhibitor is selected from compounds, their prodrugs and their pharmaceutically-acceptable salts, of the group consisting of

3-(3,4-difluorophenyl)-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;
3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxyethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide.

Claim 18. (Previously presented) The composition of Claim 9 wherein the leukocyte activation inhibitor is a cyclosporin compound.

Claim 19. (Previously presented) The composition of Claim 18 wherein the cyclosporin compound is cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl].

Claim 20. (Previously presented) A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a 5-lipoxygenase inhibitor, a cyclosporin compound and a cyclooxygenase-2 inhibitor selected from Dupont Dup 697, Taisho NS-398, meloxicam, flosulide and compounds of Formula I or a pharmaceutically salt of a compound having Formula I wherein:



(I)

wherein A is a 5-or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carbocyclic rings;

wherein R^1 is at least one substituent selected from heterocyclo, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R^2 is selected from alkyl, and amino; and

wherein R^3 is a radical selected from halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclo, cycloalkenyl, aralkyl, heterocycloalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,

arylaminocarbonyl, alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, arylamino, N-aralkylamino, N-alkyl-N-arylaminocarbonyl, alkyl-N-arylmino, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, N-aralkylaminoalkyl, alkyl-N-aralkylaminoalkyl, alkyl-N-arylminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, arylsulfonyl, alkyl-N-arylaminosulfonyl.

Claim 21. (Cancelled)

Claim 22. (New) A composition comprising:

a 5-lipoxygenase inhibitor selected from the group consisting of:

(Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide, (1-Benzo[b]thien-2-yl-ethyl)-N-hydroxyurea, 4-[2',4'-difluorobiphenyl]-4-oxomethyl-butanic acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridinyl)-2-propenamide, 1-methyl-6-[[[3-(tetrahydro-4-methoxy-2-methyl-2H-pyran-4-yl)-2-propenyl]oxy]methyl]-2(1H)-quinolinone, Hydroxy-N-[4-[3-(4-fluorophenoxy)phenyl]-3-butyn-2-yl]-urea, N-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea, [3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxyurea, (R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, [2-[[2-[(4'-fluoro[1,1'-biphenyl]-4-yl)methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxy-urea, dihydro-4-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-2H-1,2-oxazin-3(4H)-one, 4-(2-quinolylmethoxy)-N-(3-fluorobenzyl-phenyl-amino-methyl-4-benzoic-acid, 6-chloro-2,3-dimethoxynaphthalene-1,4-diol-diacetate, (2-[2-[1-(4-chlorobenzyl)-4-methyl-6-[(5-phenylpyridin-2-yl)methoxy]-4,5-dihydro-1H-thiopyrano[2,3,4-cd]indol-2-yl]ethoxy]-butanoic acid, [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl]-acetic acid, 1-([5-(3-methoxy-4-ethoxycarbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine,

2-[2,3-dihydro-1-methoxy-6-(2-naphthalenylmethoxy)-1H-inden-1-yl]-thiazole, (6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-ethyl-2-quinolone, and 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone;

a cyclooxygenase-2 inhibitor selected from the group consisting of:

3-(3,4-difluorophenyl)-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;

3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone;

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-

yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-

yl]pyridine;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-

yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-hydroxyethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and

4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl)-4-

oxazolyl]benzenesulfonamide; and

a cyclosporin compound.

Claim 23. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 3-(3,4-difluorophenyl)-4-(4-methylsulfonylphenyl)-2-(5H)-furanone.

Claim 24. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone.

Claim 25. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Claim 26. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Claim 27. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Claim 28. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine.

Claim 29. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine.

Claim 30. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide.

Claim 31. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide.

Claim 32. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-hydroxyethyl-3-phenylisoxazol-4-yl]benzenesulfonamide.

Claim 33. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide.

Claim 34. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide.

Claim 35. (New) The composition of claim 22 wherein the cyclooxygenase-2 inhibitor is 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide.

Claim 36. (New) A composition comprising 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea and a cyclosporin compound.

Claim 37. (New) A composition comprising 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea and a cyclosporin compound.

Claim 38. (New) A composition comprising 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea and a cyclosporin compound.